

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



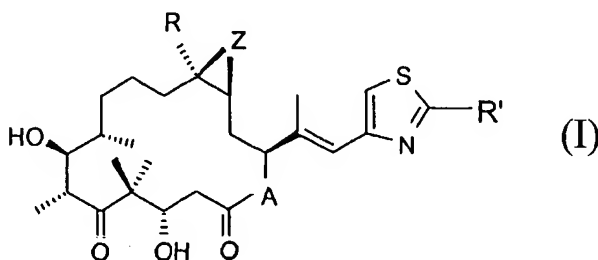
(43) International Publication Date  
29 April 2004 (29.04.2004)

PCT

(10) International Publication Number  
**WO 2004/035050 A1**

- (51) International Patent Classification<sup>7</sup>: **A61K 31/427**,  
A61P 5/00, 5/18, 35/00
- (74) Agents: **HOXIE**, Thomas et al.; Novartis AG, Corporate  
Intellectual Property, CH-4000 Basel (CH).
- (21) International Application Number:  
PCT/IB2003/004514
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,  
GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ,  
OM, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SY, TJ,  
TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.
- (22) International Filing Date: 13 October 2003 (13.10.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/418,592 15 October 2002 (15.10.2002) US
- (84) Designated States (*regional*): Eurasian patent (AM, AZ,  
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,  
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU,  
IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).
- (71) Applicant (*for all designated States except US*): **BOARD  
OF SUPERVISORS OF LOUISIANA STATE UNI-  
VERSITY AND AGRICULTURAL AND MECHANICAL  
COLLEGE** [US/US]; Office of the Vice Chancellor  
for Academic Affairs, 433 Bolivar Street, Room 824, New  
Orleans, LA 70112 (US).
- Published:**  
— with international search report
- (72) Inventor; and
- (75) Inventor/Applicant (*for US only*): **WOLTERING**, Eu-  
gene, A. [US/US]; 30 Chateau Pontet Canet, Kenner, LA  
70065 (US).
- For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: USE OF EPOTHILONE DERIVATIVES FOR THE TREATMENT OF HYPERPARATHYROIDISM



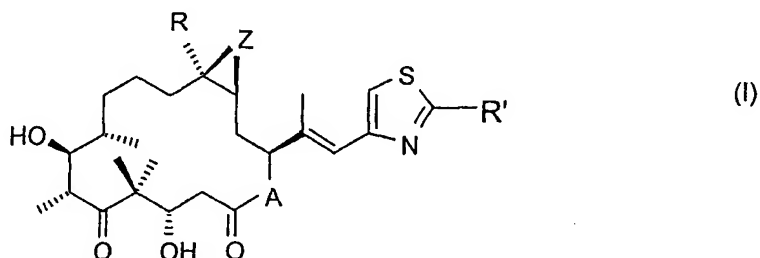
(57) Abstract: The present invention relates to a method of treating a warm-blooded animal, especially a human, having hyperparathyroidism comprising administering to said animal a therapeutically effective amount of an epothilone derivative of formula (I) or a pharmaceutically acceptable salt thereof.

## USE OF EPOTHILONE DERIVATIVES FOR THE TREATMENT OF HYPERPARATHYROIDISM

The present invention relates to a method of treating a warm-blooded animal, especially a human, having hyperparathyroidism comprising administering to said animal a therapeutically effective amount of an epothilone derivative of formula I as defined below.

The epothilones, especially epothilones A, B and D, represent a new class of microtubule stabilizing cytotoxic agents (see Gerth, K. et al., J. Antibiot. 49, 560-3 (1996); or Hoefle et al., DE 41 38 042).

Surprisingly, it was found that epothilone derivatives of formula I



wherein A represents O or  $\text{NR}_N$ , wherein  $\text{R}_N$  is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino or methylthio, and Z is O or a bond, or a pharmaceutically acceptable salt thereof, produce a beneficial effect in the treatment of hyperparathyroidism.

Hence, the invention relates to a method of treating a warm-blooded animal having hyperparathyroidism comprising administering a therapeutically effective amount of an epothilone derivative of formula I wherein A represents O or  $\text{NR}_N$ , wherein  $\text{R}_N$  is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino or methylthio, and Z is O or a bond, or a pharmaceutically acceptable salt thereof to a warm-blooded animal in need thereof.

Unless stated otherwise, in the present disclosure organic radicals and compounds designated "lower" contain not more than 7, preferably not more than 4, carbon atoms.

A compound of formula I wherein A represents O, R is hydrogen and Z is O is known as epothilone A; a compound of formula I wherein A represents O, R is methyl and Z is O is known as epothilone B; a compound of formula I wherein A represents O, R is hydrogen and Z is a bond is known as epothilone C; a compound of formula I wherein A represents O, R is methyl and Z is a bond is known as epothilone D.

Epothilone derivatives of formula I wherein A represents O or  $\text{NR}_N$ , wherein  $\text{R}_N$  is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl and Z is O or a bond, and methods for the preparation of such epothilone derivatives are in particular generically and specifically disclosed in the patents and patent applications WO 93/10121, US 6,194,181, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 and WO 00/31247 in each case in particular in the compound claims and the final products of the working examples, the subject-matter of the final products, the pharmaceutical preparations and the claims is hereby incorporated into the present application by reference to this publications. Comprised are likewise the corresponding stereoisomers as well as the corresponding crystal modifications, e.g. solvates and polymorphs, which are disclosed therein. Epothilone derivatives of formula I, especially epothilone B, can be administered in the form of pharmaceutical compositions which are disclosed in WO 99/39694.

Epothilone derivatives of formula I wherein A represents O or  $\text{NR}_N$ , wherein  $\text{R}_N$  is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methoxy, ethoxy, amino, methylamino, dimethylamino or methylthio, and Z is O or a bond, and methods for the preparation and administration of such epothilone derivatives are in particular generically and specifically disclosed in the patent application WO99/67252, which is hereby incorporated by reference into the present application. Comprised are likewise the corresponding stereoisomers as well as the corresponding crystal modifications, e.g. solvates and polymorphs, which are disclosed therein.

The transformation of epothilone B to the corresponding lactam is disclosed in Scheme 21 (page 31, 32) and Example 3 of WO 99/02514 (pages 48 - 50). The transformation of a compound of formula I which is different from epothilone B into the corresponding lactam can be accomplished analogously. Corresponding epothilone derivatives of formula I wherein  $\text{R}_N$  is lower alkyl can be prepared by methods known in the art such as a reductive alkylation reaction starting from the epothilone derivative wherein  $\text{R}_N$  is hydrogen.

The terms "treatment" or "treating" as used herein comprises the treatment of patients having hyperparathyroidism or being in a pre-stage of said disease which treatment produces one or more of the following effects in hyperparathyroidism patients:

- a reduction in parathyroid hormone levels in blood,
- a reduction in parathyroid hormone levels in urine,
- a reduction of calcium levels in blood,
- a reduction of calcium levels in urine,
- an increase in bone density.

It will be understood that in the discussion of methods, references to the active ingredients are meant to also include the pharmaceutically acceptable salts. If these active ingredients have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The active ingredients having an acid group (for example COOH) can also form salts with bases. The active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

In one preferred embodiment of the invention, an epothilone derivative of formula I is employed wherein A represents O, R is lower alkyl, especially methyl, ethyl or n-propyl, or hydrogen and Z is O or a bond. More preferably, an epothilone derivative of formula I is employed wherein A represents O, R is methyl and Z is O, which compound is also known as epothilone B.

Throughout the present specification and claims hyperparathyroidism means primary, secondary or tertiary hyperparathyroidism. Furthermore, three different forms of tertiary hyperparathyroidism are known, which are adenoma, hyperplasia and carcinoma.

Control of hypercalcemia from recurrent or persistent parathyroid adenoma, parathyroid hyperplasia, or from parathyroid carcinoma is difficult, and on occasion impossible. A number of approaches have been used to control the symptomatic hypercalcemia induced by these conditions.

The present invention pertains preferably to parathyroid adenoma, parathyroid hyperplasia and parathyroid carcinoma, more preferably, to recurrent or persistent parathyroid adenoma, parathyroid hyperplasia and parathyroid carcinoma.

The symptoms induced by hypercalcemia life can be threatening. This is particularly true of parathyroid carcinoma, where patients typically die from uncontrolled hypercalcemia.

One embodiment the present invention pertains to the control of hypercalcemia resulting from parathyroid adenoma, parathyroid hyperplasia and parathyroid carcinoma.

The method of treating a warm-blooded animal having hyperparathyroidism as disclosed herein can be employed as a monotherapy or in addition to an established therapy comprising, e.g., the administration of a standard anti-diarrheal.

The term "standard anti-diarrheal" as used herein include, but is not limited to, natural opiods, such as tincture of opium, paregoric, and codeine, synthetic opiods, such as diphenoxylate, difenoxin and loperamide, bismuth subsalicylate, octreotide, motilin antagonists and traditional antidiarrheal remedies, such as kaolin, pectin, berberine and muscarinic agents. The antidiarrheal agent is administered as a preventative measure throughout the treatment cycle or as needed when diarrhea occurs. The antidiarrheal agent is administered to prevent, control or eliminate diarrhea that is sometimes associated with the administration of epothilones, especially epothilone B.

The structure of the active ingredients identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active ingredients and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both *in vitro* and *in vivo*.

The person skilled in the pertinent art is fully enabled to select relevant test models to prove the herein before and hereinafter mentioned beneficial effects of a compound of formula I on hyperparathyroidism.

The pharmacological activity of a compound of formula I, in particular epothilone B, can be demonstrated, e.g., in a study wherein patients suffering from hyperparathyroidism are treated with continuous 4-week cycles (three weeks on/one week off) of epothilone B until either disease progression or unacceptable side effects occur. Response initially can be evaluated after the first two cycles, and can be based on unchanged or improvement in clinical symptoms. Evaluations for response can be performed, e.g., every two cycles thereafter.

It is submitted that at least part of the effect observed with the compounds of formula I on the diseases mentioned herein are resulting from the inhibition of angiogenesis. A number of *in vitro* angiogenesis assays exist, however, they do not provide potentially useful information for the treatment of an individual patient. Clonogenic assays have been utilized to evaluate the response of an individual's tumor to antineoplastic agents, but these tumor fragments are cultured in an environment that does not lead to neovessel growth. It is known that human vein disks incorporated into a 0.3% fibrin-thrombin clot will develop angiogenic vessel growth from the cut edge of the vessel disk. The *in vitro* angiogenesis assay described below can be employed to demonstrate the utility of the compounds of formula I for the treatment of the diseases mentioned herein.

**METHODS:** Tumor disks (2mm in diameter) from seven fresh surgical specimens are incorporated into fibrin-thrombin clots overlaid with nutrient medium containing 20% fetal bovine serum. The fragments are allowed to become angiogenic and on day 18, nutrient medium or nutrient medium containing a compound of formula I, is added. Tumor disks are visually assessed over time to determine the percent of wells that initiated an angiogenic response (% I). Neovessel growth, density, and length are graded at intervals using a semi-quantitative visual neovessel growth-rating scheme [angiogenic index (AI), 0-16 scale]. Statistical significance of the results is tested using comparison of two proportions for % initiation and t-tests for the angiogenic index ( $p < .05$  considered significant\*).

Novel pharmaceutical composition suitable for the treatment of hyperparathyroidism contain, for example, from about 10 % to about 100 %, preferably from about 20 % to about 60 %, of the active ingredients of formula I. Pharmaceutical preparations for enteral or parenteral administration are, for example, those in unit dosage forms, such as sugar-coated tablets,

tablets, capsules or suppositories, and furthermore ampoules. If not indicated otherwise, these are prepared in a manner known per se.

The effective dosage of a compound of formula I may vary depending on the particular compound or pharmaceutical composition employed, the mode of administration, the severity of the hyperparathyroidism being treated. Thus, the dosage of a compound of formula I is selected in accordance with a variety of factors including the route of administration and the renal and hepatic function of the patient. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of a compound of formula I required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of the active ingredients within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the active ingredients' availability to target sites.

If the the warm-blooded animal is a human, the dosage of a compound of formula I is preferably in the range of about 0.1 to 75, preferably 0.25 to 50, e.g. 2.5 or 6, mg/m<sup>2</sup> once weekly for two to four, e.g. three, weeks, followed by 6 to 8 days off in the case of an adult patient.

In one embodiment of the invention epothilone B is administered weekly in a dose that is between about 0.1 to 6 mg/m<sup>2</sup>, preferably between 0.1 and 3 mg/m<sup>2</sup>, e.g. 2.5 mg/m<sup>2</sup>, for three weeks after an interval of one to six weeks, especially an interval of one week, after the preceding treatment. In another embodiment of the invention said epothilone B is preferably administered to a human every 18 to 24 days in a dose that is between about 0.5 and 7.5 mg/m<sup>2</sup>.

In another embodiment of the invention, epothilone B is provided continuously, e.g. for a week or four weeks, at a dose that effects a blood level of 10 to 12 M or higher. Preferably, the drug is applied in that embodiment by means of a sustained release formulation.

Moreover, the present invention provides a commercial package comprising as active ingredients a compound of formula I together with instructions for use thereof in the treatment of hyperparathyroidism or of the diseases mentioned herein.

The invention also provides the use of a compound of formula I for the preparation of a medicament for the treatment of hyperparathyroidism or of the diseases mentioned herein.

#### EXAMPLE 1

The following results were obtained with epothilone B in the *in vitro* angiogenesis assay described hereinabove.

Tumor Type	% Initiation		% ↓	P <.05	AI (0-16)		% ↓	P <.05
	Control	EpoB 10 <sup>-8</sup> M			Control	EpoB 10 <sup>-8</sup> M		
Breast carcinoma	55.2	3.3	94	*	10.6	1	91	*
Bronchial carcinoid	41.7	37	12	NS	10.1	6.1	40	NS
Midgut carcinoid	23.3	20	15	NS	13.7	8.2	40	*
Midgut carcinoid (met)	41.4	0	100	*	8.6	0	100	*
Thyroid cancer	100	50	50	*	14.1	2.1	85	*
Renal cell carcinoma	60	6.7	88	*	4.9	1	80	*
Thymic carcinoid	8.3	3.3	40	NS	9.2	2.5	73	NS
Mean +/- SEM	47.1 ± 11.1	17.2 ± 7.4	60 ± 14	-	10.2 ± 1.2	3 ± 1.1	73 ± 9	-

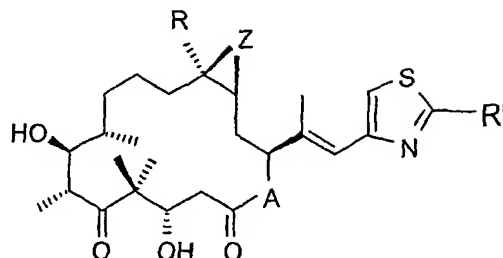
**RESULTS:** All tumors initiated an angiogenic response *in vitro*. The mean percent of wells that initiated an angiogenic response was 47.1 ± 11.1% in this group of tumors. A thymic carcinoid was the least angiogenic (8.3% of wells initiated), while a thyroid cancer, which was identified as a parathyroid adenoma, exhibited 100% initiation. Following initiation, tumors exhibited progressive increases in neovessel growth, length, and density over time. The mean angiogenic index of these tumors was 10.2 ± 1.2. Treatment of these tumors with 10<sup>-8</sup> M epothilone B significantly decreased (60 ± 13.8%) the initiation of their angiogenic response. Subsequent vessel development was also significantly inhibited (73 ± 9%) by epothilone B treatment.



CONCLUSIONS: Epothilone B may be an effective antiangiogenic agent in a variety of tumor types. The employed *in vitro* model provides useful information to the clinician on the effect of specific antiangiogenic agents on an individual patient's tumor. This may be particularly useful in patients with tumors that, as a group, are unresponsive to treatment with antineoplastic agents.

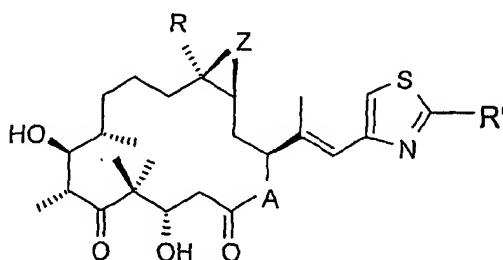
What is claimed

1. The use of a compound of formula I



wherein A represents O or  $\text{NR}_N$ , wherein  $\text{R}_N$  is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino or methylthio, and Z is O or a bond, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of hyperparathyroidism.

2. A method of treating a warm-blooded animal having hyperparathyroidism comprising administering a therapeutically effective amount of an epothilone derivative of formula I

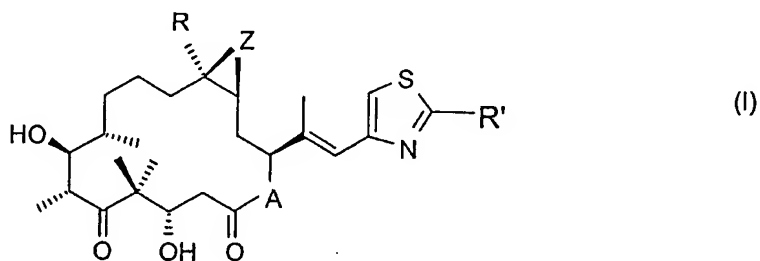


(I)

wherein A represents O or  $\text{NR}_N$ , wherein  $\text{R}_N$  is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino or methylthio, and Z is O or a bond, or a pharmaceutically acceptable salt thereof to a warm-blooded animal in need thereof.

3. The method according to claim 2 wherein the warm-blooded animal is a human.

4. The method according to claim 2 in which method an epothilone derivative of formula I wherein A represents O, R is methyl and Z is O or a pharmaceutically acceptable salt thereof is administered to a warm-blooded animal in need thereof.
5. The method according to claim 4 comprising administering said epothilone derivative weekly in a dose that is between about 0.1 to 6 mg/m<sup>2</sup> for three weeks after an interval of one to six weeks after the preceding treatment.
6. The method according to any one of claims 2 to 5 wherein the hyperparathyroidism disease is adenoma, hyperplasia or carcinoma.
7. The method according to claim 6 wherein the disease is parathyroid adenoma, parathyroid hyperplasia or parathyroid carcinoma.
8. The method according to any one of claims 2 to 5 wherein the parathyroid cancer disease is recurrent or persistent parathyroid adenoma, recurrent or persistent parathyroid hyperplasia or recurrent or persistent parathyroid carcinoma.
9. The method according to any one of claims 2 to 5 wherein the hyperparathyroidism disease is primary or secondary hyperparathyroidism.
10. A method for the treatment of hypercalcemia resulting from parathyroid adenoma, parathyroid hyperplasia or parathyroid carcinoma comprising administering a therapeutically effective amount of an epothilone derivative of formula I



wherein A represents O or  $\text{NR}_N$ , wherein  $\text{R}_N$  is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino or methylthio, and Z is O or a bond,  
or a pharmaceutically acceptable salt thereof to a warm-blooded animal in need thereof.

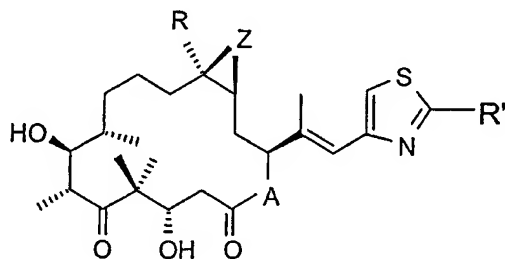
11. The method according to claim 10 wherein the warm-blooded animal is a human.

12. The method according to claim 10 in which method an epothilone derivative of formula I wherein A represents O, R is methyl and Z is O or a pharmaceutically acceptable salt thereof is administered to a warm-blooded animal in need thereof.

13. The method according to claim 12 comprising administering said epothilone derivative weekly in a dose that is between about 0.1 to 6  $\text{mg}/\text{m}^2$  for three weeks after an interval of one to six weeks after the preceding treatment.

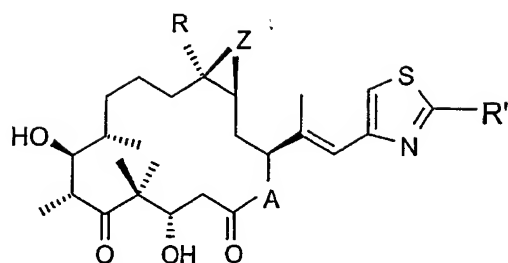
14. The method according to to any one of claims 10 to 13 wherein the disease is recurrent or persistent parathyroid adenoma, recurrent or persistent parathyroid hyperplasia or recurrent or persistent parathyroid carcinoma.

15. A pharmaceutical composition comprising a quantity of compound of formula I



wherein A represents O or  $\text{NR}_N$ , wherein  $\text{R}_N$  is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino or methylthio, and Z is O or a bond, or a pharmaceutically acceptable salt thereof, which is therapeutically effective against hyperparathyroidism.

16. A commercial package comprising a compound of formula I



wherein A represents O or NR<sub>N</sub>, wherein R<sub>N</sub> is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino or methylthio, and Z is O or a bond, or a pharmaceutically acceptable salt thereof, together with instructions for use thereof in the treatment of hyperparathyroidism.

## INTERNATIONAL SEARCH REPORT

International Classification No.

PCT/IB 03/04514

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/427 A61P5/00 A61P5/18 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, MEDLINE, CHEM ABS Data, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/39694 A (NOVARTIS ERFIND VERWALT GMBH ; HOOGEVEST PETER VAN (CH); NOVARTIS AG ( ) 12 August 1999 (1999-08-12) cited in the application claims 1-14	15,16
A	the whole document	1-13
X	WO 98/22461 A (BIOTECHNOLOG FORSCHUNG GMBH ; GERTH KLAUS (DE); HOFLE GERHARD (DE); R) 28 May 1998 (1998-05-28) cited in the application * claims 1-17 *	15,16
A	the whole document	1-13
X	WO 99/67252 A (NOVARTIS ERFIND VERWALT GMBH ; NOVARTIS AG (CH); VALLBERG HANS (SE); N) 29 December 1999 (1999-12-29) cited in the application	15,16
A	the whole document	1-13

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

22 January 2004

Date of mailing of the international search report

30/01/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk-  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Uiber, P

## INTERNATIONAL SEARCH REPORT

 International Application No  
 PCT/IB 03/04514

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9939694	A	12-08-1999	AU 753519 B2 17-10-2002
			AU 2722699 A 23-08-1999
			BE 1012140 A3 02-05-2000
			BR 9907647 A 14-11-2000
			CA 2320182 A1 12-08-1999
			CN 1292683 T 25-04-2001
			WO 9939694 A2 12-08-1999
			EP 1052974 A2 22-11-2000
			FR 2774909 A1 20-08-1999
			HU 0101564 A2 28-11-2001
			ID 26549 A 18-01-2001
			IT MI990208 A1 05-08-1999
			JP 2002502810 T 29-01-2002
			NO 20003930 A 04-10-2000
			NZ 506389 A 25-07-2003
			PL 342629 A1 18-06-2001
			SK 11702000 A3 18-01-2001
			TR 200002299 T2 21-11-2000
			TW 457095 B 01-10-2001
			US 2003203876 A1 30-10-2003
			ZA 9900874 A 05-08-1999
WO 9822461	A	28-05-1998	AU 753546 B2 24-10-2002
			AU 5483798 A 10-06-1998
			BR 9713363 A 25-01-2000
			CA 2269118 A1 28-05-1998
			CN 1237970 A 08-12-1999
			CZ 9901750 A3 15-09-1999
			WO 9822461 A1 28-05-1998
			EP 1367057 A1 03-12-2003
			EP 0941227 A1 15-09-1999
			HU 0000497 A2 28-06-2000
			IL 129558 A 31-10-2001
			JP 2001504474 T 03-04-2001
			KR 2000053308 A 25-08-2000
			NO 992338 A 14-05-1999
			NZ 335383 A 27-10-2000
			PL 333435 A1 06-12-1999
			RU 2198173 C2 10-02-2003
			TW 408119 B 11-10-2000
			ZA 9710384 A 18-05-1999
WO 9967252	A	29-12-1999	US 6380394 B1 30-04-2002
			AU 757854 B2 06-03-2003
			AU 4774899 A 10-01-2000
			AU 4775299 A 10-01-2000
			BR 9911420 A 20-03-2001
			CA 2334342 A1 29-12-1999
			CN 1306531 T 01-08-2001
			WO 9967252 A2 29-12-1999
			WO 9967253 A2 29-12-1999
			EP 1089998 A2 11-04-2001
			HU 0102711 A2 28-12-2001
			JP 2002518504 T 25-06-2002
			NO 20006378 A 21-02-2001
			NZ 508622 A 25-07-2003
			PL 345327 A1 17-12-2001
			SK 19712000 A3 11-09-2001

# INTERNATIONAL SEARCH REPORT

International: PCT/IB 03/04514  
 lication No

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9967252	A	TR 200003844 T2	20-04-2001
		US 2003203938 A1	30-10-2003
		US 6531497 B1	11-03-2003
		ZA 200007059 A	30-01-2002
<hr/>			